Thesis title: Design of prodrugs of antiviral molecules targeting the central nervous system to treat neurotropic viruses.

Laboratory: AFMB, Architecture and Function of Biological Macromolecules, URM 7257.
Team : Replicases Virales : Structure, mechanism and Drug-design (Dir : Dr Bruno Canard).
Thematic Group : Antiviral Medicinal Chemistry, led by Dr Karine Alvarez.

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Background to the study

Viruses responsible for neurological disorders, such as certain Bunya- Corona- or Flaviviruses, are a real public health problem due to the lack of effective antiviral molecules. Neurologically-tropic viral infections are the most difficult to treat, and therapeutic developments are hampered by the problem of delivering the antiviral to the central nervous system (CNS). Nucleotide analogues (NAs) are the main therapeutic arsenal used clinically to treat viral infections, although their delivery to the brain is limited by the passage of the blood-brain barrier and the blood-cerebrospinal barrier. Although the delivery of AN to the CNS has been improved by the study of metabolizing enzymes, endogenous cellular transport systems, and the synthesis of conjugates, chemical delivery devices and prodrugs, it is still insufficient. In the current context, there is an urgent need to propose solutions for the design of a new generation of CNS-targeted AN prodrugs.

Project description

This multi-disciplinary project covers several areas, two of which will be developed within the framework of this thesis project.

Missions

One is linked to the study of the metabolism of several antiviral molecules of the NA type, repositioned on Bunya- Corona- and Flavivirus infections, which have shown therapeutic interest and whose understanding will be a major asset for the design of improved ANs. The other axis is linked to the rational design, synthesis and study of new ANs prodrugs to improve CNS targeting.

Candidate profil

With an engineering or Master's degree, the candidate should have a strong background in organic synthesis (medicinal chemistry), with a motivation to tackle complementary drug-design disciplines such as biophysics, biochemistry and crystallography.

Keywords

Medicinal chemistry, antivirals, prodrugs, nucleotide analogues, metabolism.

Bibliographic references

1) Chazot A. et al. In Review, Plos Biology, 2024. The activation chain of the broad-spectrum antiviral Bemnifosbuvir at atomic resolution. 2) Shannon A. et al. NAR, 2023, DOI : 10.1093/nar/gkad1194. An exonuclease-resistant chain-terminating nucleotide analogue targeting the SARS-CoV-2 replicase complex.3) Feracci M. et al. Antivir Res, 2023, DOI :10.1016/J.antiviral.2023.105574. AT-752 multiple sites and activities on the dengue virus replication enzyme NS5.